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Abstract: Three-point mutations (R117H, N211, A16V) within the cationic trypsinogen gene have been identified in patients with hereditary pancreatitis (HP). A genetic background has also been discussed for idiopathic juvenile chronic pancreatitis (IJCP), which closely mimicks the clinical pattern of HP, and alcoholic chronic pancreatitis because only a small number of heavy drinkers develop pancreatitis. This prompted us to screen 104 patients in our well-defined pancreatitis cohort for the currently known cationic trypsinogen gene mutations. The R117H mutation was detected in seven patients (six patients of two clinically classified HP families, one patient with clinically classified IJCP) and the A16V mutation in one IJCP patient. No cationic trypsinogen gene mutations were found in the remaining 96 patients with chronic and recurrent acute pancreatitis of various etiologies. Our results demonstrate the need for genetic testing to exclude HP, particularly in the presence of an atypical or unknown family history. In addition, cationic trypsinogen gene mutations are no predisposing factor in patients with chronic and recurrent acute pancreatitis of different etiologies.

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Trypsinogen Gene Mutations in Patients with Chronic or Recurrent Acute Pancreatitis

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Summary: Three-point mutations (R117H, N21I, A16V) within the cationic trypsinogen gene have been identified in patients with hereditary pancreatitis (HP). A genetic background has also been discussed for idiopathic juvenile chronic pancreatitis (IJCP), which closely mimicks the clinical pattern of HP, and alcoholic chronic pancreatitis because only a small number of heavy drinkers develop pancreatitis. This prompted us to screen 104 patients in our well-defined pancreatitis cohort for the currently known cationic trypsinogen gene mutations. The R117H mutation was detected in seven patients (six patients of two clinically classified HP families, one patient with clinically classified IJCP) and the A16V mutation in one IJCP

patient. No cationic trypsinogen gene mutations were found in the remaining 96 patients with chronic and recurrent acute pancreatitis of various etiologies. Our results demonstrate the need for genetic testing to exclude HP, particularly in the presence of an atypical or unknown family history. In addition, cationic trypsinogen gene mutations are no predisposing factor in patients with chronic and recurrent acute pancreatitis of different etiologies. **Key Words:** Cationic trypsinogen gene mutation—Hereditary pancreatitis—Idiopathic juvenile chronic pancreatitis—Alcoholic chronic pancreatitis—Recurrent acute pancreatitis.

In industrialized countries, chronic pancreatitis (CP) is caused by long-term alcohol abuse in approximately 70% of patients (1,2). Other causes of CP are rare (e.g., heredity, hyperlipidemia and hypercalcemia). In 10–30% of cases, the cause of CP remains undetermined (1,2). Irrespective of the etiology, the clinical pattern of CP is characterized by an early stage with recurrent episodes of acute pancreatitis (AP) followed by a late stage with steatorrhea, diabetes mellitus, and pancreatic calcifications in most patients (2).

The pathogenesis of CP is unclear, and it is unknown whether there are factors common to the etiologically different forms of CP (3). It is assumed that autodigestion secondary to intraglandular activation of trypsinogen is a primary event in AP. The underlying etiology-specific mechanism remains unknown, however (3,4).

Hereditary pancreatitis (HP) offers the possibility to study the pathophysiology of CP. HP is an autosomal disorder with 80% penetrance and variable expressivity (4). To date, in the CT gene, two-point mutations in exon 2 (N21I) and 3 (R117H), respectively, have been identified in several families with HP, suggesting a genetic basis for the development of HP (4,5). Recently, a second mutation in exon 2 (A16V) of the CT gene was described in patients with both positive and negative family history of CP (6).

At present, it is not clear whether CT gene mutations are also found in nonhereditary CP (e.g., idiopathic CP [ICP] and alcoholic CP [ACP]). Clinically, ICP comprises two subgroups: a juvenile type (IJCP), with an average age at onset of approximately 25 years, and a senile type (ISCP), with the first clinical manifestations at the age of approximately 60 years. These two subgroups of ICP, first clinically characterized 20 years ago and confirmed in a recent study at the Mayo Clinic (7), appear to be two distinct entities with presumably different etiopathogeneses. IJCP closely mimicks the clinical pattern of HP suggestive of a genetic basis, i.e., onset

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of recurrent AP in childhood or adolescence and progression to CP. In contrast to HP, there is no clinical evidence of heredity in IJCP (7).

A genetic background for ACP has been postulated based on (i) isolated reports of familial clustering (8), (ii) recent studies on mutations of the cystic fibrosis gene in a CP series of different etiologies, including ACP (9,10), and (iii) the fact that only 5–10% of heavy drinkers develop pancreatitis that may progress to ACP.

In most studies published to date, only patients of HP families were investigated. The aim of the present study was to determine the frequency of CT gene mutations in our large series of clinically well-defined patients with CP, including IJCP, HP, and ACP, and recurrent AP.

METHODS

Definitions

The diagnosis of CP was based on a typical history and one or more of the following criteria: pancreatic calcifications, typical histology, persistent exocrine insufficiency, and/or pancreatic steatorrhea (fecal chymotrypsin test <120 µg/g for at least 2 years, fecal fat >7 g/24 h). Data from each patient on the clinical history, including onset of pancreatitis, etiology, hospitalization, histopathology, and previous control studies were reviewed. Alcohol was considered causative in patients with a daily intake of >80 g of ethanol for at least 5 years. Alcohol consumption was documented by interviews of the patient, family members, and social workers. Patients with no or irregular minimal alcohol intake were classified as idiopathic after the exclusion of other rare causes (e.g., heredity, hyperlipidemia, hypercalcemia, abdominal trauma, or previous radiation therapy). Follow-up is defined as the time period from clinical onset, i.e., the first episode of pancreatitis to the last consultation.

Patients

Between January 1 and December 31, 1998, an ethylenediaminetetraacetic acid (EDTA) blood sample for DNA analysis was obtained at the annual consultation from all consecutive patients enrolled in our long-term pancreatitis study (11). In addition, blood samples were collected from members of HP families through their family physician. All patients with HP and IJCP gave informed consent to the DNA analysis.

The group with clinically classified HP comprised three families (10 individuals tested). In one family (Ko), two siblings and their deceased mother had CP. In a second family (Da), previously described (12), four patients with calcified CP (IV/2, IV/3, V/1, V/4) and two asymptomatic individuals (V/2, V/3) were available for

analysis. The patient IV/1 and IV/4 have died from lung and pancreatic cancer, respectively. In a third family (Ta), two brothers had calcified CP; their father with recurrent AP died at the age of 44 years from unknown cause.

Clinical evidence of familial aggregation of CP was noted in three families with proven ACP: (i) one family with two brothers who had definite ACP (one has died); (ii) a second family with two brothers with ACP and their father who had a pancreatic pseudocyst, and (iii) a third family with two brothers, one with calcified ACP, one with recurrent abdominal pain suggestive of pancreatitis who committed suicide, and their deceased father who had diabetes mellitus. Blood samples from each patient (alive, with definite ACP) of the three families were available for DNA analysis.

DNA analyses

EDTA blood samples were stored at 4°C before processing at the Department of Internal Medicine II, University of Freiburg. DNA was purified from blood samples using the QiaAmp Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's recommendation. Exon 3 sequences of the CT gene were amplified using polymerase chain reaction (PCR) primers 5'-GGTCCTGGGTCTCATACCTT-3' (forward) and 5'-GGGTAGGAGGCTTCACACTT-3' (reverse; amplification conditions: initial 5-minute denaturation step at 94°C, followed by 30 cycles at 94°C for 30 seconds; 64°C for 30 seconds; 72°C for 1 minute, and a final 7-minute elongation step at 72°C). According to Whitcomb et al. (5), as a consequence of the G to A change in position 117, a novel restriction site for Afl III is found. Therefore, the PCR products were digested with Afl III overnight and analyzed by 1% agarose gel electrophoresis. To detect the N21I mutation, the exon 2 sequences of the CT gene were amplified by seminested PCR, using primers 5'-CCCAAATCTTGCAATTTGAC-3' (forward outer primer) and 5'-ACAGTTAGCAGAGGTAGAGTG-3' (reverse outer and inner primer) for the first reaction (amplification conditions: initial 5-minute denaturation step at 94°C, followed by 20 cycles at 94°C for 30 seconds; 55°C for 30 seconds; 72°C for 2 minutes, and a final 7-minute elongation step at 72°C) and 5'-GCTGCCCCCTTTGATGATGAT-3' (forward inner primer) for the second amplification (amplification conditions: initial 5-minute denaturation step at 94°C, followed by 20 cycles at 94°C for 30 seconds; 55°C for 30 seconds; 72°C for 30 seconds, and a final 7-minute elongation step at 72°C). The PCR product was purified with a PCR purification kit according to the manufacturer's recommendation (QIA-

Quick PCR purification Kit; Qiagen). To detect the A to T change in position 21 of exon 2, the purified PCR fragment was sequenced using the forward inner primer (Cycle Sequencing Kit; Amersham, Buckinghamshire, England). A DNA sample from a patient with a known N21I mutation was obtained from V. Keim (13) and served as a positive control. To detect the A16V mutation in exon 2, primers were designed as published by Witt et al. (6): (5'-CGCCACCCCTAACATGCTAT-3', forward; 5'-CTCTCCCAGGCAGACT GGCC-3' reverse; amplification conditions: the initial 5-minute denaturation step at 94°C, followed by 30 cycles at 94°C for 30 seconds, 64°C for 30 seconds, 72°C for 30 seconds, and a final 7-minute elongation step at 72°C). To identify the loss of the restriction site for Fnu4HI owing to the C to T change in codon 16, the PCR products were digested overnight and analyzed with 1.5% agarose gel electrophoresis.

Statistical analyses

Statistical analyses were performed to compare the data of the three subgroups ACP, IJCP, and HP. All analysis were done using the StatView 4.51 statistical software package (Abacus Concepts, Berkeley, CA). Nominal data were analyzed using χ^2 test and Fisher's exact test when appropriate. *p* Values for pairwise comparisons were adjusted using the Bonferroni correction. Continuous variables were analyzed using simple analysis of variance followed by pairwise comparisons using the Bonferroni-Dunn test and are presented as mean \pm standard deviation. A *p* value of <0.05 was considered significant.

RESULTS

Clinical characteristics

A total of 104 patients (92 with CP, 12 with recurrent AP) were enrolled in the present study. The clinical char-

acteristics of the patients are summarized in Table 1. The two subgroups with HP and IJCP differ from the rest of the cohort, especially ACP, with respect to gender distribution and the low mean age at clinical onset of disease. Pancreatic calcifications, exocrine insufficiency, and diabetes mellitus are noted in a high percentage, irrespective of the etiology. HP patients have a significantly lower mean age at onset compared to IJCP patients. HP patients had the longest follow-up. A logistic regression identified both the age and etiology as independent factors for the incidence of diabetes mellitus.

Studies of the cationic trypsinogen gene

The results of the DNA analyses in the 104 patients are shown in Table 2. Two asymptomatic members of the HP family Da (V/2 and V/3, Fig. 1) and three (mother, two siblings) and four (mother, father, two siblings) asymptomatic family members of the two IJCP patients who tested positive for the R117H and A16V mutation, respectively (see below), were also tested.

In two families (Ko, Da) with clinical HP, the R117H mutation was identified. All members with this mutation had clinically documented CP except for a 20-year-old woman (V/2, Fig. 1). In a third family (Ta), no CT gene mutation in exons 2 and 3 was found in two brothers with definite CP.

In the cohort of nonalcoholic/nonhereditary CP, the R117H mutation in the CT gene was detected in one patient clinically classified as having IJCP. This family (father, mother, and two siblings) had no exocrine insufficiency (fecal chymotrypsin test) in 1974. A re-evaluation of the patients history with the help of several family members revealed clinical evidence suggestive of recurrent pancreatitis in some individuals of the maternal kindred but no definite CP. DNA analysis of blood samples from the mother and two siblings revealed no R117H mutation. Because the patient's father had died at

TABLE 1. Clinical characteristics of patients with chronic (CP) and recurrent acute pancreatitis (AP)

Etiology	No. of pts	Sex [m/f]	Age at onset [years]*	Calcification [No. of pts (%)]	Exocrine insufficiency [No. of pts (%)]	Diabetes mellitus [No. of pts (%)]	Follow-up [years]*
Hereditary CP	8	4/4 ^c	11.4 \pm 5.9 ^c	7 (88)	6 (75)	4 (50)	31.3 \pm 14.4 ^c
Alcoholic CP	58	55/3 ^c	34.3 \pm 7.0 ^c	46 (79)	56 (97)	47 (81) ^c	20.7 \pm 6.6
Non-alcoholic CP	26						
idiopathic-juvenile	16	9/7 ^b	21.1 \pm 6.8 ^{ab}	11 (69)	13 (81)	3 (19) ^b	19.0 \pm 11.5 ^a
idiopathic-senile	4	4/0	57.3 \pm 7.1	4 (100)	4 (100)	2 (50)	18.0 \pm 8.8
rare causes**	6	4/2	35.3 \pm 15.8	4 (67)	5 (83)	3 (50)	20.3 \pm 12.5
Recurrent AP***	12	11/1	34.2 \pm 17.0	0 (0)	0 (0)	2 (17)	20.2 \pm 7.0

No. of pts: number of patients; CP, chronic pancreatitis; AP, acute pancreatitis; *: mean value \pm SD; **: postradiation 2; hyperlipidemia 1, hyperparathyroidism 1, unknown 2; ***: biliary 4, alcoholic 4, idiopathic 2, hyperlipidemia 1, posttraumatic 1.

^a *p* < 0.05 IJCP vs. HCP^o.

^b *p* < 0.05 IJCP vs. ACP^o.

^c *p* < 0.05 HCP vs. ACP^o.

^o after Bonferroni correction.

TABLE 2. Mutations in the cationic trypsinogen gene in our cohort with chronic (CP) and recurrent acute pancreatitis (AP)

	No. of Pts	Mutation		
		Exon 3	Exon 2	
		R117H	N21I	A16V
Hereditary CP	8	6	0	0
Alcoholic CP	58	0	0	0
Non-alcoholic CP				
idiopathic-juvenile	16	1	0	1
idiopathic-senile	4	0	0	0
rare causes*	6	0	0	0
Recurrent AP*	12	0	0	0

*: etiology as in Table 1.

the age of 60 years and no other available family members were available for testing, the paternal kindred could not be investigated. This patient's 8-year-old son, however, has had recurrent abdominal pain since the age of 4 years and is positive for the R117H mutation. In another patient clinically classified as having IJCP, the A16V mutation was detected. This patient's family has no history or clinical evidence of pancreatitis. DNA analysis performed on both parents and one sibling revealed this mutation in the patient's mother and the sibling.

All remaining patients with CP caused by alcohol use and rare causes or recurrent AP were negative for all these mutation, including the patients with ACP associated with a suggestive family history.

DISCUSSION

The investigation of our large series of unselected consecutive CP patients was aimed at determining the prevalence of the currently known CT gene mutations in various forms of CP. Compared to most previous studies investigating affected members of HP families only, our analysis included patients from our clinically well-defined pancreatitis cohort followed for more than 30 years (11). The analysis was performed for the two known mutations of the CT gene in HP families and the recently described signal peptide cleavage site mutation of this gene (4–6).

In our series, members of two of three clinically classified HP families revealed the R117H mutation, whereas no mutation was detected in the third family. These results confirm previous studies that suggest locus heterogeneity but no racial specificity of CT gene mutations in HP kindreds (4,13–15). In the study by Whitcomb et al. (5) comprising 206 individuals from 25 families with clinically symptomatic HP, 96 (47%) were negative for both mutations, indicating that HP may be

associated with genes other than the CT gene. Indeed, in a large family (J) in this study, HP was linked to a new locus on chromosome 12 (16). All our HP patients, except one with a documented mutation, had a typical history of recurrent pancreatitis and progression to definite CP. One CT gene mutation-positive individual is still asymptomatic at the age of 21 years, supporting the previously reported high but incomplete penetrance of the trait (17,18). Furthermore, additional pathogenetic factors such as pregnancy may be important in HP (19).

IJCP is a subgroup of idiopathic CP. Despite no family history of pancreatitis in patients with IJCP, the early onset of recurrent pancreatitis suggests a possible genetic defect (7,20). Of our 16 patients with IJCP, 14 were negative for the three CT gene mutations. However, in two patients, either a R117H or an A16V mutation was detected, emphasizing the need for genetic testing to rule out HP. In three unaffected family members (mother, two siblings) of the patient positive for the R117H mutation, this mutation was not found. The deceased father was asymptomatic for pancreatic disease like other members of this kindred. Thus, the mode of inheritance remains unknown in this patient. A *de novo* R117H mutation is possible. Interestingly, a review of this patient's family history revealed that his 8-year-old son has recurrent abdominal pain and is positive for the R117H mutation. Unfortunately, no clinical tests for CP have been done on this child because the father has so far refused medical care for his son. In contrast to the high penetrance of the R117H mutation, the A16V mutation was detected in two asymptomatic first-degree relatives (mother, brother) of our patient positive for this mutation. In addition, there is no history of pancreatitis in untested family members of the maternal kindred. Thus, there must be a low penetrance of this mutation and other (genetic) defects in this patient with IJCP.

No CT gene mutations were found in our patients with CP of alcoholic, idiopathic-senile or rare type, or recurrent acute pancreatitis. In particular, genetic testing was negative in two brothers with pancreatitis owing to familial hyperlipidemia and in four members with familial clustering of ACP. Recently, evidence for a genetic link between idiopathic or alcoholic CP and cystic fibrosis (9,10,21,22) or α 1-antitrypsin (α 1-AT) deficiency was presented (23,24). The majority of these studies are based on small series and preliminary analysis. These results should be interpreted with caution because mutations of the CFTR or α 1-AT genes are common in the general population in contrast to CT gene mutations. In addition, the selection of patients is difficult because there exists no standardized nomenclature for CP. Both facts suggest a selection bias.

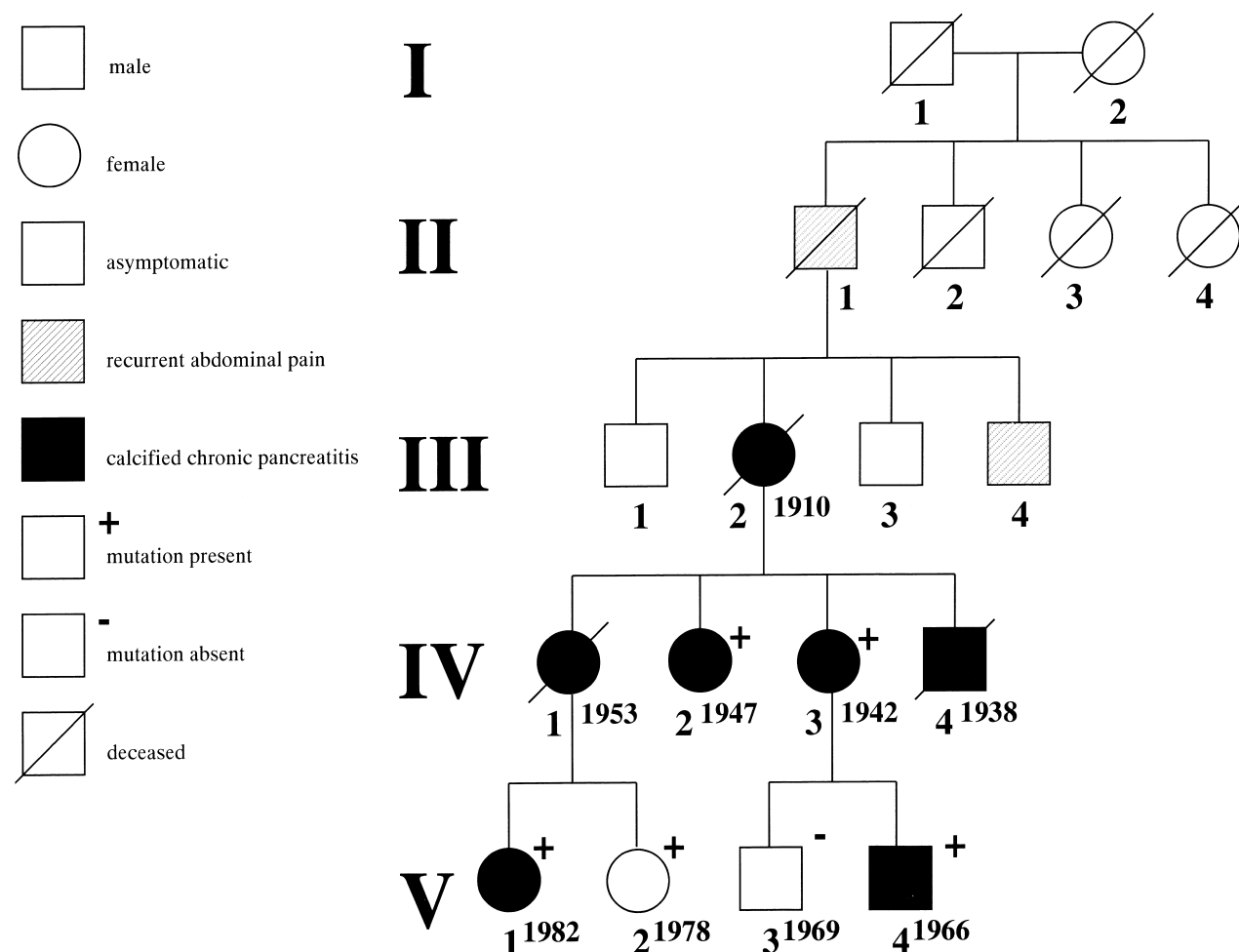


FIG. 1. Pedigree of a family with HP caused by the R117H mutation of the cationic trypsinogen gene.

The results from our studies allow several major conclusions: Genetic testing is appropriate in patients with ICP, particularly in the presence of an atypical or unknown family history. The currently known CT gene mutations are not predisposing genetic factor in patients with ACP. Our results therefore support the concept that different mechanisms and cofactors have to be considered in the pathogenesis of nonhereditary CP. Furthermore, in vitro and in vivo models are needed to define the pathogenesis of HP in patients with CT gene mutations. Further genetic analyses should identify novel genes and mutations in patients with HP negative for the known CT gene mutations. Finally, studies of patients with well-defined CP of various etiologies are needed to determine the relevance of CT gene mutations and to identify cofactors responsible for the progression to CP.

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